SUPPORTIVE CARE

Defibrotide for the Treatment of Hepatic Veno-Occlusive Disease: An Update from the International Compassionate Use Program in 710 Patients

Selim Corbacioglu1, Enric Carreras2, Mohamad Mohy3, Antonio Pagliuca4, Maria Ballabio5, Robin Hume6, Valeria Bandiera2, Giorgia Finetto2, Paul C. Richardson7.

1University of Regensburg, Regensburg, Germany; 2Josep Carreras Foundation & Research Institute, Barcelona, Spain; 3Hospital Saint-Antoine, Paris, France; 4King’s College Hospital, London, United Kingdom; 5Gentium S.p.A., Villa Guardia, Italy; 6Jazz Pharmaceuticals, Inc., Palo Alto, CA; 7Dana-Farber Cancer Institute, Boston, MA

Introduction: Hepatic veno-occlusive disease (VOD, or sinusoidal obstruction syndrome) is a potentially fatal complication of stem cell transplantation (SCT). Severe VOD (sVOD) is usually characterized by multi-organ failure (MOF) and >80% mortality. Defibrotide (DF) is approved in the EU for the treatment of sVOD in SCT. We report the final results of a large, international compassionate use program (CUP; 1998-2009) in Europe, the US, Asia, and the Middle East.

Methods: DF was provided on a compassionate basis or via single patient (pt) emergency-use requests post-SCT or chemo-/radiotherapy. Eligibility, DF use, safety, and outcomes were collected with case record forms. In the US, pts met Baltimore criteria for VOD and had MOF. At other sites, pts met Seattle or Baltimore, ultrasound, and/or histological criteria. Initial dosing recommendation was 10 mg/kg/d (4 divided doses/d IV) titrated up to 60 mg/kg/d based on tolerability/response. Following results of a US Phase 2 study, the recommended dose was 25 mg/kg/d. Treatment duration was up to investigators. Data included adverse events (AEs) and survival at Day+100 post-SCT or start of chemo-/radiotherapy.

Results: Safety/outcome data were submitted voluntarily for 710 pts receiving ≥1 DF dose. VOD developed post-SCT in 89% (71% allogeneic; 16% autologous; 2% missing), and post-chemo-/radiotherapy in 11%. Median age was 25 (range, 0.2-70) years; 43% were <18 years. Median days to VOD onset was 13. Symptoms were bilirubin >2 mg/dL (88% of patients), weight gain >5% (82%), hepatomegaly (77%), ascites (67%), right upper quadrant pain (64%), and MOF (41%). Per Bearman criteria or MOF, 60% had sVOD.

The median dose was 25 mg/kg/d given for a median of 15 d.

AEs were reported in 378 pts (53%; <20% related); most were serious (364) and fatal (350). Causes of death were generally reported as AEs; hence the most common new or worsening AEs were MOF (144, all fatal), VOD (79, 78 fatal), and sepsis (49, 48 fatal). Serious AEs/fatalities were generally similar across doses. Hemorrhage was reported by 85 pts (55 serious, including 37 fatal), most commonly gastrointestinal (33) or respiratory (24). Central nervous system (CNS) hemorrhage was reported in 10 pts. Respiratory tract hemorrhage was highest in the 60/80 mg/kg/d dose group (9%) vs lower doses (<5%), but gastrointestinal and CNS hemorrhages were similar across doses (<6%). Withdrawals due to an AE (63) were mostly due to hemorrhage (50), primarily gastrointestinal (22).

The Kaplan-Meier (KM) estimate of Day+100 survival was 54%. The figure shows KM survival curve by dose group; in the 25 mg/kg/d group (the approved EU dose) estimated survival was 58% at Day+100 (Figure 1).

Conclusions: DF was generally well tolerated in this large CUP; AEs were typical for VOD pts. Consistent with prior studies, survival was 54% at Day+100. Subgroup analyses support 25 mg/kg/d as the optimal dose.

Support: Jazz Pharmaceuticals

Preliminary Results from the AdVise Study Evaluating Brincidofovir (CMX001, BCV) for the Treatment of Disseminated and High-Risk Adenovirus (AdV) Infection

Michael S. Grimley1, Gabriela M. Marón2, Vinod K. Prasad3, David A. Jacobsohn4, Jo-Anne H. Young5, Greg Chittick6, Thomas M. Brundage6, Hervé Momméja-Marin6. 1Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2St. Jude Children’s Research Hospital, Memphis, TN; 3Pediatric BMT Program, Duke University Medical Center, Durham, NC; 4Chief, Division of Blood and Marrow Transplantation, Children’s National Medical Center, Washington, DC; 5University of Minnesota, Minneapolis, MN; 6Chimerix, Inc., Durham, NC

Background: AdV is associated with significant morbidity and mortality. No drug is currently approved for AdV. BCV is an orally available lipid-conjugate of cidofovir (CDV) that has demonstrated promise as preemptive therapy in allo HCT patients (pts) with asymptomatic AdV viremia (VL) in a Phase 2 study. The pilot portion of a Phase 3 BCV study for AdV (CMX001-304, AdVise Study; NCT02087306) was initiated in MAR2014. Preliminary results for 26 subjects enrolled through 15JUL2014 are described (data cut-off 12SEP2014).

Methods: All subjects receive open-label BCV 100 mg (≥ 50 kg) or 2 mg/kg (< 50 kg) twice a week.

Results: For the 26 subjects, median age = 6.5 y (range: 0-29), 58% < 12 y; 20 allo HCT pts (16 with disseminated disease), 4 solid organ transplant pts and 2 chemotherapy pts; median VL in plasma by quantitative polymerase chain reaction (PCR) at baseline (BL) 4.8 log_{10} copies/mL (range: undetectable [< 2 log_{10}; < LOD] to > 10 log_{10} (n = 23); 46% were AdV positive in respiratory secretions, 58% in
Changes in Plasma AdV Viremia Over Time: All Subjects (N = 23)

Figure 1.

Joseph H. Antin 1, Leslie E. Lehmann 9, Valeria Bandiera 8, Robin Hume 10, Alison Hannah 10, Bijan Nejadnik 10, Robert J. Soiffer 7, the Defibrotide Study Group 1, Jerome Lipper Multiple Myeloma Center, Division of Hematologic Malignancy, Department of Medical Oncology, Dana-Farber Cancer Center, Harvard Medical School, Boston, MA; 2 Division of Blood and Marrow Transplantation, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; 3 Bone Marrow Transplantation and Cellular Therapy, St Jude Children’s Research Hospital, Memphis, TN; 4 Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY; 5 Pediatrics/Division of Oncology, The Children’s Hospital of Philadelphia, Philadelphia, PA; 6 Division of Blood and Marrow Transplantation, Stanford University Medical Center, Stanford, CA; 7 Stem Cell/Bone Marrow Transplantation Program, Division of Hematologic Malignancy, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; 8 Center for Stem Cell Transplantation, Division of Hematologic Malignancy, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; 9 Gentium S.p.A., Villa Guardia, Italy; 10 Jazz Pharmaceuticals, Inc., Palo Alto, CA

Introduction: Severe hepatic veno-occlusive disease (VOD, also called sinusoidal obstruction syndrome) with multi-organ failure (MOF) is a life-threatening complication of hematopoietic stem cell transplant (HSCT), with a mortality rate of >80%. Defibrotide has a protective effect on injured endothelium and restores thrombo-fibrinolytic balance. In severe VOD, defibrotide improves complete response (CR) rates and survival at Day+100 post-HSCT, with a favorable safety profile. In the EU, defibrotide is approved for treatment of severe hepatic VOD in HSCT therapy in adults and children. In the US, there are no approved therapies for VOD; however, defibrotide is available through an expanded access, protocol-directed treatment IND (T-IND). The T-IND gathers data on safety/efficacy of defibrotide in patients (pts) with severe and non-severe VOD post-HSCT, as well as post-chemotherapy (CT) alone.

Methods: The original T-IND protocol required VOD diagnosed by Baltimore criteria (total bilirubin ≥2.0 mg/dL with ≥2 of hepatomegaly, ascites, or 5% weight gain) with MOF (renal and/or pulmonary failure) following HSCT; the study was amended to include non-severe VOD (defined as no MOF) post-HSCT or post-CT. Exclusion criteria include clinically significant bleeding or need for >1 vasopressor. Defibrotide was given as a 2-hour infusion at 6.25 mg/kg IV q6h (25 mg/kg/d) for a recommended ±21 days.

Results: This interim safety analysis update is based on 612 pts enrolled from December 2007 to December 2013 (including 99 in 2013) who received ≥1 defibrotide dose. Median patient age was 12 years (range <0.1–69).

Overall, ≥1 treatment emergent adverse event (AE) was reported in 454 pts (74.2%). Of these, 138 pts (22.5%) had AEs possibly, probably, or definitely related to defibrotide. Related AEs in >2.0% included pulmonary hemorrhage (4.7%), gastrointestinal hemorrhage (3.6%), epistaxis (3.1%), and hypotension (2.8%). Serious AEs (SAEs) were reported by 368 pts (60.1%) and most were assessed as not related to defibrotide; 82 pts (13.4%) had an SAE at least possibly related to study treatment, most commonly pulmonary hemorrhage (3.9%) and gastrointestinal hemorrhage (2.9%). AEs leading to death occurred in 254 pts (41.5%); these AEs were deemed possibly related to study medication in only 17 pts (2.8%).

Previously reported efficacy data at Day+100 in 425 evaluable pts showed survival of 55% (by Kaplan-Meier...